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Studies on Intestinal Lymphatic Absorption of Drugs. I. Lymphatic Absorption of Alkyl Ester Derivatives and α-Monoglyceride Derivatives of Drugs

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Several alkyl ester derivatives or α-monoglyceride derivatives of ^{3}H-labeled compounds, *i.e.* trimetoquinol, TA-594, acetaminophen, naproxen and nicotinic acid, were synthesized and administered orally to rats cannulated in the thoracic duct. The radioactivity appearing in 24 h-lymph was measured and analyzed by thin-layer chromatography.

Most of the α-monoglyceride derivatives were absorbed *via* the intestinal lymphatic system, while the alkyl esters were very poorly absorbed. After oral administration of α-monoglyceride derivatives of labeled naproxen and nicotinic acid, the radioactive compounds found in the lymph were mainly monoglyceride, diglyceride and triglyceride analogues, while in plasma the main radioactive compound was the parent drug.

It was concluded that α-monoglyceride derivatives of drugs were absorbed *via* the lymphatic system and transported into blood, yielding the parent drug in blood.

Keywords — lymphatic absorption; α-monoglyceride derivative; trimetoquinol; acetaminophen; naproxen; nicotinic acid

Introduction

The oral route is the safest and most convenient method to administer drugs the patients. Most drugs, after oral administration, are absorbed *via* the portal system delivered directly to the liver, metabolized in the liver and then the products and unmetabolized drug are distributed over the whole body. Although this may be the most conventional way of drug distribution, other ways also exist and deserve consideration. One of them, lymphatic transport of drugs, has not been widely investigated. Up to now, a few compounds such as 3-methylcholanthrene,[1] asarone,[2] naftifine[3] and LK-903[4,5] have been shown to be absorbed *via* the lymphatic system. If drugs which are absorbed *via* the portal system, are modified and absorbed exclusively *via* the lymphatic system of the gut, such a pathway for drugs would be of benefit:

(1) Since the rate of lymphatic flow is approximate 1/1000 to 1/500 times that of portal blood flow, the absorption of the drug would be slower and result in a longer half-life of drug in the vascular system.
(2) Since drugs absorbed *via* the lymphatic system are transported directly into the blood *via* the vena subclavia, the drugs will be distributed in the whole body without suffering first-pass metabolism by the liver.
(3) The absorption rate of drugs with poor intestinal absorbability will increase.
(4) In the case when the drug causes side-effects such as gastrointestinal ulceration or hemorrhage, its therapeutic ratio of the pharmacological action to side-effect will increase by chemically blocking the functional group.

Two methods of introducing drugs into the lymphatic absorption route can be considered. One is the pharmaceutical preparation of drugs as lipid emulsions and mixed micelles[6-10] and another is the chemical modification of drugs, although there is little known about this method.[11]

In this study, using trimetoquinol (a bronchodilator), TA-594 (an anodyna), acetaminophen (an anodyna), naproxen (an anti-inflammatory agent) and nicotinic acid (a hypolipidemic agent) as model drugs, their alkyl ester derivatives and α-monoglyceride derivatives were synthesized and the lymphatic absorption of these derivatives was examined in rats cannulated in the thoracic duct. Fundamental aspects of chemical modifications to enhance lymphatic transport of drugs are discussed.

Materials and Methods

Labeled Compounds — The ^{3}H-labeled compounds of TA-594 and trimetoquinol (both developed in this company), nicotinic acid (Tokyo Kasei Co., Ltd.) and naproxen (kindly supplied by Syntex Co., Ltd.) were prepared by catalytic hydrogenation[12] of the respective brominated compounds with tritium gas (100 mCi–1 Ci, NEN Research Products). Their specific activities were 1.6, 3.7, 0.7 and 0.6 mCi/mg, respectively. The radiochemical purities of these ^{3}H-compounds were more than 98%. ^{3}H-Acetaminophen was prepared by N-acetylation[13] of *p*-aminophenol (Tokyo Kasei Co., Ltd.) with ^{3}H-acetic anhydride (50 mCi/mmol, NEN Research Products). The specific activity was 10.5 μCi/mg and the radiochemical purity was more than 98%.

Alkyl Ester Derivatives: Ester derivatives of ^{3}H-TA-594 were prepared[14] by condensation of ^{3}H-TA-594 with *n*-capryl chloride and myristoyl chloride, and the specific activities were 56 and 48 μCi/mg, respectively. Their radiochemical purities were both more than 98%. ^{3}H-Naproxen myristate was synthesized from ^{3}H-naproxen and myristyl alcohol, and ^{3}H-trimetoquinol dibutyrate synthesized previously[15] was purified by thin layer chromatography (TLC) (solvent system: chloroform – *n*-butanol – acetic acid – water (5 : 1 : 1 : 1, v/v)). The specific activities were 210 and 1.1 μCi/mg, respectively, and the radiochemical purities of both were more than 98%. Structural formulae of the drugs and their alkyl ester derivatives are shown in Fig. 1.

Glyceride Derivatives: α',β-Isopropylidene-α-alkanoyl glycerides [I_n], used as a carrier compound in the preparation of α-monoglyceride derivatives, were synthesized in our Organic Chemistry Research Laboratory.

a) α-^{3}H-Acetaminophen Glyceryl Decyl Ether (α-^{3}H-AGE10): Methylsulfonyl chloride (0.13 ml) was added to a solution of compound [$I_{n=10}$] (1 mmol) and triethylamine (0.22 ml) in CH_2Cl_2 (5 ml) at −5 – 10 °C. After stirring for 5 min, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. Removal of the solvent gave methylsulfonate of [$I_{n=10}$]. ^{3}H-Acetaminophenol (1.0 mmol) was added to a suspension of sodium hydride (1.1 mmol) in DMF (3 ml) at 0 °C, after stirring for 2 h. A solution of methylsulfonate of [$I_{n=10}$] in DMF (2 ml) was added and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. Removal of the solvent gave compound [$II_{n=10}$]. Twenty percent formic acid/ethanol (0.5 ml) was added to a solution of compound [$II_{n=10}$] in ethanol (1 ml) and the mixture was refluxed for 2 h. The product, α-^{3}H-AGE10, was purified by silica gel column chromatography (cyclohexane–acetone (4:5,

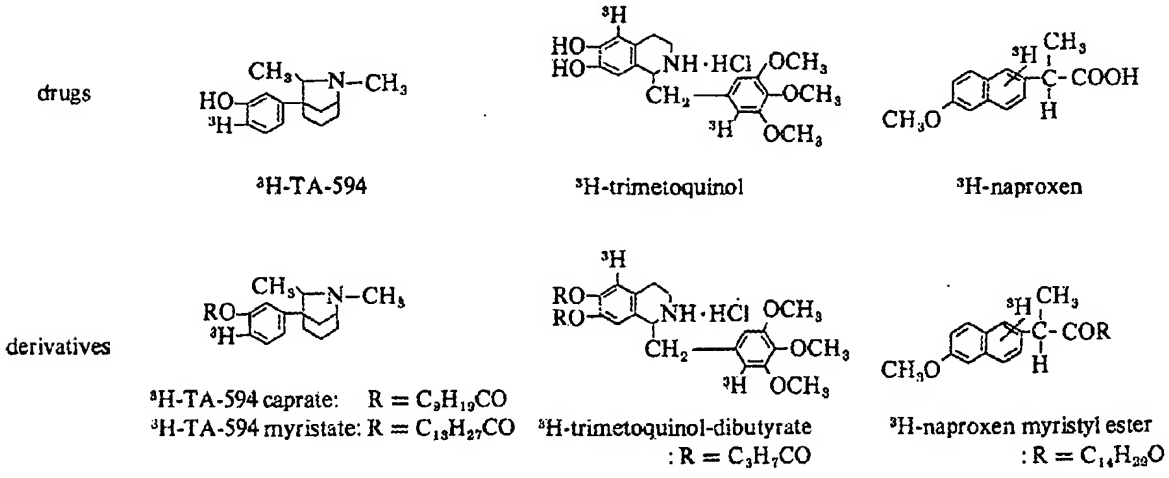

Fig. 1. Structural Formulae of Drugs and Their Alkyl Ester Derivatives

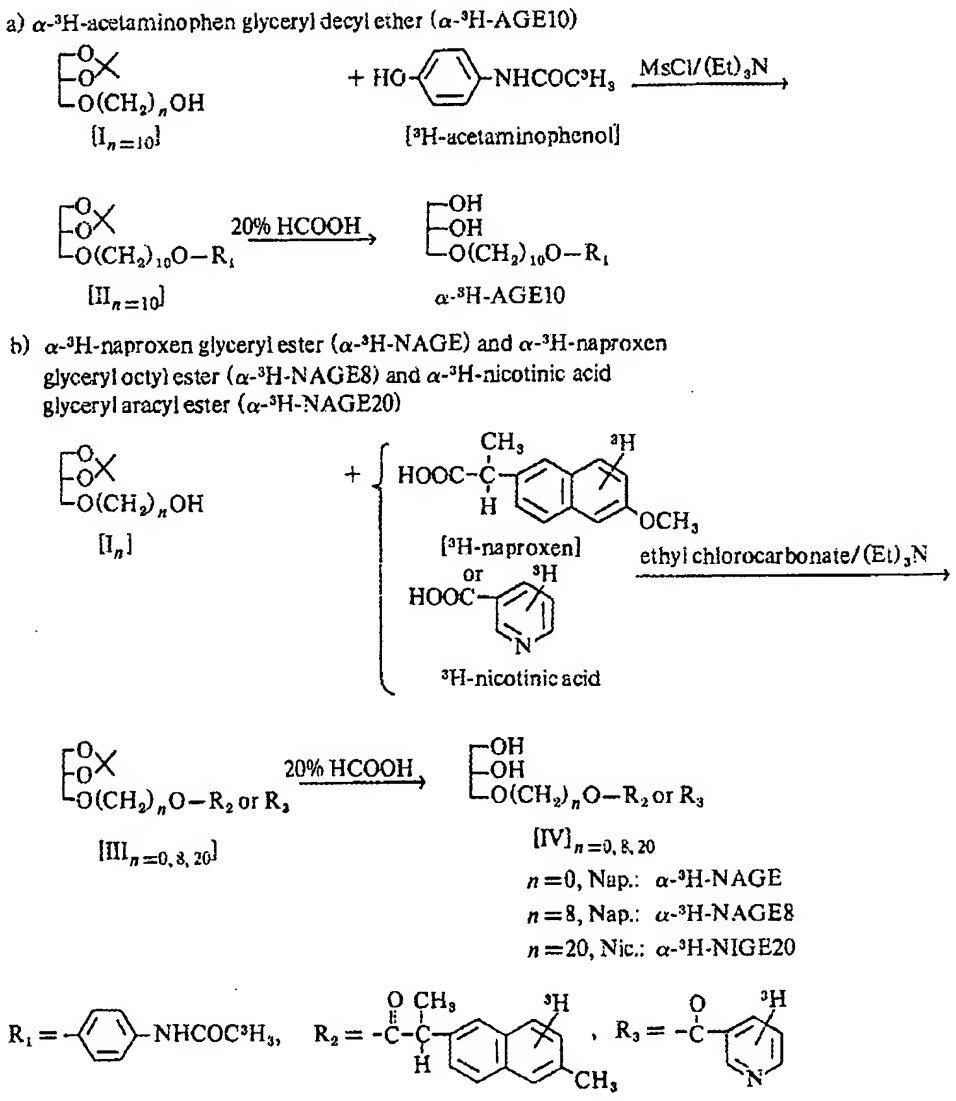

Fig. 2. Synthetic Route and Labeled Position of Glyceride Derivatives of Drugs

v/v) as an eluent). The specific activity was 0.5 μCi/mg and the radiochemical purity was more than 97%.

b) α-³H-Naproxen Glyceryl Ester (α-³H-NAGE), α-³H-Naproxen Glyceryl Octyl Ester (α-³H-NAGE8) and α-³H-Nicotinic Acid Glyceryl Arachyl Ester (α-³H-NIGE20): α-³H-NAGE, α-³H-NAGE8 and α-³H-NIGE20 were synthesized from ³H-naproxen or ³H-nicotinic acid according to the synthetic route shown in Fig. 2[16] and their specific activities were 163, 115 and 133 μCi/mg, respectively. Their radiochemical purities were all greater than 98%. All compounds were characterized by NMR and MS.

Animals and Administration — Male Sprague Dawley rats (9 weeks old, weighing 300—350 g) were employed. Each drug or its derivatives was suspended with equimolar lecithin (from Soybean, Tokyo Kasei Co., Ltd., assuming that m.w. is 750) in distilled water using a sonicator (Tomy UR 150P) and administered orally to rats.

The dose of each drug or its derivatives is presented in Tables I and II.

Determination of Radioactivity and Analy-

sis of Labeled Compounds in Blood and Lymph — ^{3}H-Naproxen or α-^{3}H-naproxen glyceryl octyl ester (α-^{3}H-NAGE8) was administered orally to rats and blood was collected at various times by cutting the carotid artery. Radioactivity in blood, after oxidation to ^3H_2O with an automatic combustion apparatus (Model 305, Packard), was measured with a liquid scintillation spectrometer (Model LSC-502, Aloka). To determine ^{3}H-naproxen concentrations in blood, the radioactive compounds were extracted three times with 5 volumes of ethylacetate and extracts were applied on thin-layer plates (Merck: Kieselgel 60 F_{254}, 0.25 mm thickness) and developed with the solvent systems of benzene–tetrahydrofuran–acetic acid (60 : 12 : 1, v/v) and ether–*n*-hexane–acetic acid–methanol (15 : 85 : 2 : 3, v/v). After the plates were dried, the area of ^{3}H-naproxen and other radioactive spots were scraped off from the plate into a counting vials and radioactivity was measured in the usual manner. The area under blood concentration-time curve from zero to 8 h (AUC_{0-8h}) was calculated by using the trapezoidal rule.

Labeled compounds were administered to rats cannulated in the thoracic duct[4] and the lymph was collected at various times. Radioactivity in the lymph was measured and then the lymphatic labeled constituents were analyzed by TLC as previously described.[4]

Results

Lympthatic Absorption of Alkyl Ester Derivatives

The lymphatic absorption rates of the alkyl ester derivatives of labeled TA-594, trimetoquinol and naproxen in rats are shown in Table I. When the alkyl ester derivatives of TA-594 or trimetoquinol were administered, less than 3% of the dose appeared in the lymph for 24 h in both cases. However, a relatively large quantity (11.5% of the dose) was absorbed *via* the lymphatic system after administration of the myristyl ester derivative of naproxen.

Lymphatic Absorption of α-Monoglyceride Derivatives

The lymphatic absorption rates of the α-monoglyceride derivatives of labeled acetaminophen, naproxen and nicotinic acid in rats are shown in Table II. The absorption rate of the α-naproxen glyceryl ester (α-NAGE) was only 2.3% of the dose for 24 h. On the other hand, the absorption rates of α-acetaminophen glyceryl decyl ether (α-AGEl0), which was modified by an *n*-alkyl chain ($C_{n=10}$) between acetaminophenol and glycerol, were 13.8 and 15.2% when administered at the dose of 2.5 and 25 mg/kg, respectively. The absorption rates of α-naproxen glyceryl octyl ester (α-NAGE8) and α-nicotinic acid glyceryl arachyl ester (α-NIGE20) were 28.3 and 7.4% of the dose, respectively. The α-monoglyceride derivatives of

TABLE I. Recovery of Radioactivity in Thoracic Duct Lymph after Oral Administration of Drugs or Its Alkyl Ester Derivatives

Compounds	Dose	% absorbed radioactivity in 24 h-lymph
^{3}H-TA-594	5 mg/kg ($n=3$)	1.2±0.2
^{3}H-Trimetoquinol	2.5 mg/kg ($n=2$)	1.5
^{1}H-Naproxen	12.5 mg/kg ($n=2$)	2.7
^{3}H-TA-594-Caprate	5 mg/kg ($n=3$)	2.5±0.3
	50 mg/kg ($n=4$)	1.6±0.2
^{3}H-TA-594-Myristate	5 mg/kg ($n=3$)	1.7±0.1
	50 mg/kg ($n=4$)	2.4±0.5
^{3}H-Trimetoquinol-dibutyrate	2.5 mg/kg ($n=2$)	1.9
^{3}H-Naproxen-myristate	100 mg/kg ($n=2$)	11.5

Each value represents the mean or mean ± S.E. of 2—4 animals.
Each value in parentheses represents the number of animals.

TABLE II. Recovery of Radioactivity in Thoracic Duct Lymph after Oral Administration of Drugs or Their α-Monoglyceride Derivatives

Compounds	Dose	% absorbed radioactivity in 24 h-lymph
^{3}H-Acetaminophenol	2.5 mg/kg ($n=2$)	0.8
^{3}H-Naproxen	12.5 mg/kg ($n=2$)	2.7
^{3}H-Nicotinic acid	8.7 mg/kg ($n=3$)	1.1±0.3
α-^{3}H-Acetaminophen glyceryl decyl ether (α-^{3}H-AGE10)	2.5 mg/kg ($n=2$)	13.8
	25 mg/kg ($n=2$)	15.2
α-^{3}H-Naproxen glyceryl ester (α-^{3}H-NAGE)	25 mg/kg ($n=3$)	2.3±0.2
α-^{3}H-Naproxen glyceryl octyl ester (α-^{3}H-NAGE8)	25 mg/kg ($n=3$)	28.3±3.6
α-^{3}H-Nicotinic acid glyceryl arachyl ester (α-^{3}H-NIGE20)	32 mg/kg ($n=3$)	7.4±2.8

Each value represents the mean or mean ± S.E. of 2—3 animals.
Each value in parentheses represents the number of animals.

TABLE III. Distribution of ^{3}H Radioactivity in the Lymph after Oral Administration of α-^{3}H-Naproxen Glyceryl Octyl Ester (α-^{3}H-NAGE8)

Time (h)	% Total ^{3}H-activity in lymph lipids			
	Monoglyceride (NAGE8)	Diglyceride	Triglyceride	Others
0—2	10.9	56.2	32.3	0.6
2—4	1.0	39.6	58.0	1.4
4—6	4.0	42.0	52.8	1.2
6—24	5.0	47.9	45.1	2.0

Each value represents the mean of 3 animals.

TABLE IV. Distribution of ^{3}H Radioactivity in the Lymph after Oral Administration of α-^{3}H-Nicotinic Acid Glyceryl Arachyl Ester (α-^{3}H-NAGE20)

Time (h)	% Total ^{3}H-activity in lymph lipids			
	Monoglyceride (NIGE20)	Diglyceride	Triglyceride	Others
0— 2	31.5	56.4	9.2	2.9
2— 4	30.2	45.8	23.1	0.9
4— 6	28.9	27.2	41.5	2.4
6—24	20.4	15.2	62.1	2.3

Each value represents the mean of 3 animals.

drugs in which an n-alkyl chain (C_n) was introduced between glycerol and drug were absorbed *via* the intestinal lymphatic system.

Radioactive Compounds in the Lymph

Radioactive compounds in the lymph after oral administration of α-^{3}H-NAGE8 and α-^{3}H-NIGE20 are shown in Tables III and IV, respectively. Major radioactive compounds in the

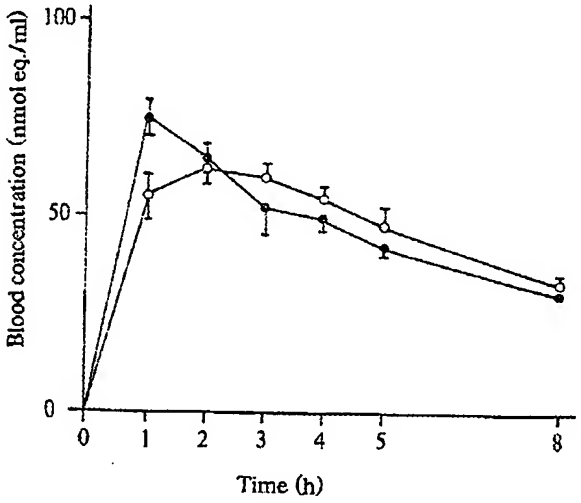

Fig. 3. Blood Concentration of Radioactivity after Oral Administration of ^{3}H-Naproxen and α-^{3}H-Naproxen Glyceryl Octyl Ester (NAGE8) to Rats (Dose: 50 μmol/kg)
—○—, α-^{3}H-NAGE8; —●—, ^{3}H-naproxen.
Each plot represents the mean ± S.E. of 3 animals.

lymph were the monoglyceride (unchanged compound), diglyceride and triglyceride analogues in both cases. After administration of α-^{3}H-NAGE8, the monoglyceride analogue was less than 10.9% of the lymph radioactivity over 24 h, and after the administration of α-^{3}H-NIGE20, the monoglyceride analogue was 20.4—31.5%.

Concentration of Radioactivity and the Radioactive Compounds in Blood

The concentrations of radioactivity in blood after oral administration of ^{3}H-naproxen and α-^{3}H-NAGE8 to rats are shown in Fig. 3. After oral administration of ^{3}H-naproxen, the radioactivity level in blood reached the maximum at 1 h, 75.2 nmol as equivalent to ^{3}H-naproxen/ml, then decreased to 51.9 nmol eq/ml at 3 h. The value of AUC_{0-8h} was 370.3 nmol·h/ml. In the case of α-^{3}H-NAGE8, the radioactivity level in blood was 54.8 nmol eq/ml at 1 h and reached the maximum, 62.3 nmol eq/ml at 2 h and this level was continued for an addition 1 h. The value of AUC_{0-8h} was 374.7 nmol·h/ml. The absorption of α-NAGE8 was slightly slower than that of naproxen. In the case of both naproxen and its derivative, more than 84% of radioactivity in blood was extracted with ethyl acetate and the main radiactive compound was found to be free ^{3}H-naproxen. Four hours after oral administration of α-^{3}H-NAGE8, unchanged α-NAGE8, was only less than 0.2% of radioactivity in blood (Table V).

Discussion

Many drugs are absorbed *via* the portal system, and some nutrients are absorbed *via* the portal system or the lymphatic system. Fat[17], cholesterol[18] and fat soluble vitamins[19-20] are known to be absorbed to a large extent via the lymphatic system. The mechanisms of fat and cholesterol absorption are well known. Lipids are hydrolyzed partially in the small intestine and the liberated fatty acids and β-monoglycerides enter into epithelium cells.

TABLE V. Distribution of ^{3}H Radioactivity in the Blood after Oral Administration of α-^{3}H-Naproxen Glyceryl Octyl Ester (α-^{3}H-NAGE8) and ^{3}H-Naproxen

	Time (h)	% Total ^{3}H-activity in blood			
		Naproxen	6-DMN *a)*	α-NAGE8	Others
α-^{3}H-NAGE8 group	1	97.1	0.7	0.2	2.0
	2	98.5	0.5	0.1	0.9
	3	97.5	0.4	0.1	2.0
	4	97.5	1.0	0.1	1.4
H-Naproxen group	1	94.6	1.4	—	4.0
	2	92.5	1.4	—	6.1
	3	95.4	1.2	—	3.4

a) 6-DMN, 6-demethyl naproxen (main metabolite of Naproxen).
Each value represents the mean 3 animals.

Within the cells, fatty acids and β-monoglycerides are biosynthesized to di- and triglycerides and subsequently, chylomicrons are formed and released into the lymph. On the other hand, cholesterol enters into epithelium cells and a large part of cholesterol is biosynthesized to cholesterol ester. The biosynthesized cholesterol ester subsequently forms chylomicrons with fatty acids, glycerides and lipoprotein and the chylomicrons are released into the lymph. In both cases, the formation of chylomicrons is considered to be a most important rate-determining step of lymphatic absorption.

When we attempted to design drugs for absorption *via* the lymphatic system, the use of these two lymphatic absorption modes were considered.

1. For examples of the absorption process of cholesterol, the alkyl ester derivatives of TA-594, trimetoquinol and naproxen were examined. Only naproxen myristate was transported into lymphatics with little or no transport of other compounds. For greater lymphatic transport, a definite range of strong lipophilicity of the derivatives may be necessary. But it is difficult to find a suitable derivative with limited range of lipophilicity for each compound.

2. For examples of the absorption process of lipid, the α-monoglyceride derivatives of acetaminophen, naproxen and nicotinic acid were examined. Most derivatives were transported into lymphatics. Therefore, it appeared relatively easy to modify drugs to derivatives with limited lipid solubility, by selecting the length of the *n*-alkyl chain to be introduced between the glycerol and the drug. The lypophilicity appears to determine the degree of lymphatic absorption. It is concluded that the α-monoglyceride derivatives are absorbed *via* the intestinal absorption system of free fatty acids or those glycerides in the manner as that of LK-903,[4] which is easily hydrolyzed to the parent drug in blood.

Moreover, when α-^{3}H-NAGE8 was administered orally to rats, the lymphatic absorption rate was 28.3% of the dose. The time found for the blood concentrations of naproxen to peak was 2 h which was 1 h later than that when ^{3}H-naproxen was administered. The value of AUC_{0-8h} of naproxen was similar to that after administration of ^{3}H-Naproxen. These results may be explained by the following: 1) Naproxen is absorbed slowly from the digestive tract, because the time for the blood concentration of naproxen to peak was 1 h. 2) Naproxen is poorly metabolized since the main radioactive compound in blood was naproxen. 3) Naproxen produced from α-^{3}H-NAGE8 by hydrolysis in the intestinal tract is absorbed *via* the portal system.

It has been reported[16,23-28] that the triglyceride derivatives of drugs when aspirin, indomethacin and naproxen were introduced directly into the β-position of the triglyceride, appeared to reduce side-effects and increased the therapeutic ratio of the pharmacological action to the side-effect. In most of these reports, no reference was made to lymphatic absorption. Therefore, the modification of drugs to their α-monoglyceride derivatives will be a very effective method of preparing prodrugs of such drugs that have only a short duration of pharmacological effect, suffer extensive first-pass metabolism in the liver, cause gastric irritation or are absorbed only to a small extent.

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